Multiple organ failure: What you need to know

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ABSTRACT: Multiple organ failure (MOF) remains a significant challenge for the acute care surgeon, often leading to poor patient outcomes. This comprehensive review explores the etiology, pathophysiology, clinical presentation, diagnosis, management strategies, prognosis, and prevention strategies associated with MOF and chronic critical illness. Understanding the intricate etiology and pathophysiology of MOF and chronic critical illness is essential for effectively managing these syndromes and developing targeted treatment strategies aimed at mitigating the underlying inflammatory, immune, and microvascular disturbances, in order to redirect patients onto a trajectory of recovery. (*J Trauma Acute Care Surg.* 2024;97: 831–838. Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Multiple organ failure; chronic critical illness; immune dysfunction.

Multiple organ failure (MOF) is a multifaceted clinical syndrome that remains one the most challenging conditions faced by acute care surgeons and surgical intensivists.[1–3] Multiple organ failure is characterized by the concomitant dysfunction of two or more organ systems, and its development marks a pivotal change in the trajectory and outcomes of critically ill surgical patients. This syndrome can be triggered by a variety of significant physiologic insults, including traumatic injury, sepsis, and extensive surgical procedures, underscoring the intricate interplay between pathophysiological mechanisms, individual patient factors, and clinical sequelae. Chronic critical illness (CCI) describes an extended phase of persistent organ dysfunction associated with poor long-term outcomes and sustained needs for intensive levels of care.[4–6] With advances in the care of critically ill surgical patients, CCI has emerged as a primary phenotype of morbidity and mortality for patients that develop MOF.[7] This introduces additional complexity and necessitates the thoughtful formulation and study of long-term management strategies for these patients.

At its foundation, MOF is precipitated by an exacerbated systemic inflammatory response to an acute insult, catalyzing a sequence of pathobiological events that encompass cellular injury, dysregulation of the immune response, and microvascular disturbances. Analogously, CCI is characterized by protracted inflammation and immune dysregulation, and recurrent nosocomial infections culminating in the need for prolonged medical intervention and resulting in unfavorable long-term outcomes.[8] The clinical manifestations and the degree of organ dysfunction associated with these conditions span a broad spectrum, from subtle symptoms such as respiratory compromise to grave complications like cardiovascular collapse, mirroring the complexity and heterogeneity of the underlying pathobiological landscape.

This review seeks to summarize the intricate dimensions of MOF and CCI, delving into their etiologies, pathobiological underpinnings, clinical presentations, diagnostic methodologies, therapeutic strategies, prognostic considerations, preventive approaches, and future considerations. By providing a comprehensive examination of these factors, the objective is to provide the reader with the essential information required to deliver optimal clinical care and improve patient outcomes of critically ill trauma and surgical patients who develop MOF and CCI.

ETIOLOGY AND PATHOPHYSIOLOGY OF MOF AND CCI

Multiple organ failure can be triggered by a variety of precipitating conditions that lead to reduced end-organ perfusion, subsequent ischemia-reperfusion injuries, and ultimately result organ failure as a result of a number of initiating factors[1,9] (Fig. 1). In parallel, CCI emerges in a subset of patients who survive the acute phase of critical illness but continue to suffer from persistent organ dysfunction, requiring long-term medical support and suffer poor long-term outcomes.[5]

In the context of sepsis, the body's overwhelming release of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, triggers a systemic inflammatory response syndrome (SIRS), characterized by endothelial cell activation, white blood cell recruitment, and initiation of thromboinflammatory pathways.[10–13] This inflammatory response is a precursor to development of MOF and a key factor in the ultimate development of CCI, where the ongoing inflammatory state and immune dysregulation contribute to sustained organ dysfunction and increased vulnerability to secondary infections and other complications.[14–16]

Trauma and major surgical interventions can precipitate MOF by activating inflammation and coagulation pathways, especially in individuals with pre-existing comorbid conditions or those encountering complications after injury or surgery.[1] Ischemia-reperfusion injuries, akin to reperfusion in conditions like myocardial infarction or organ transplant, exacerbate tissue

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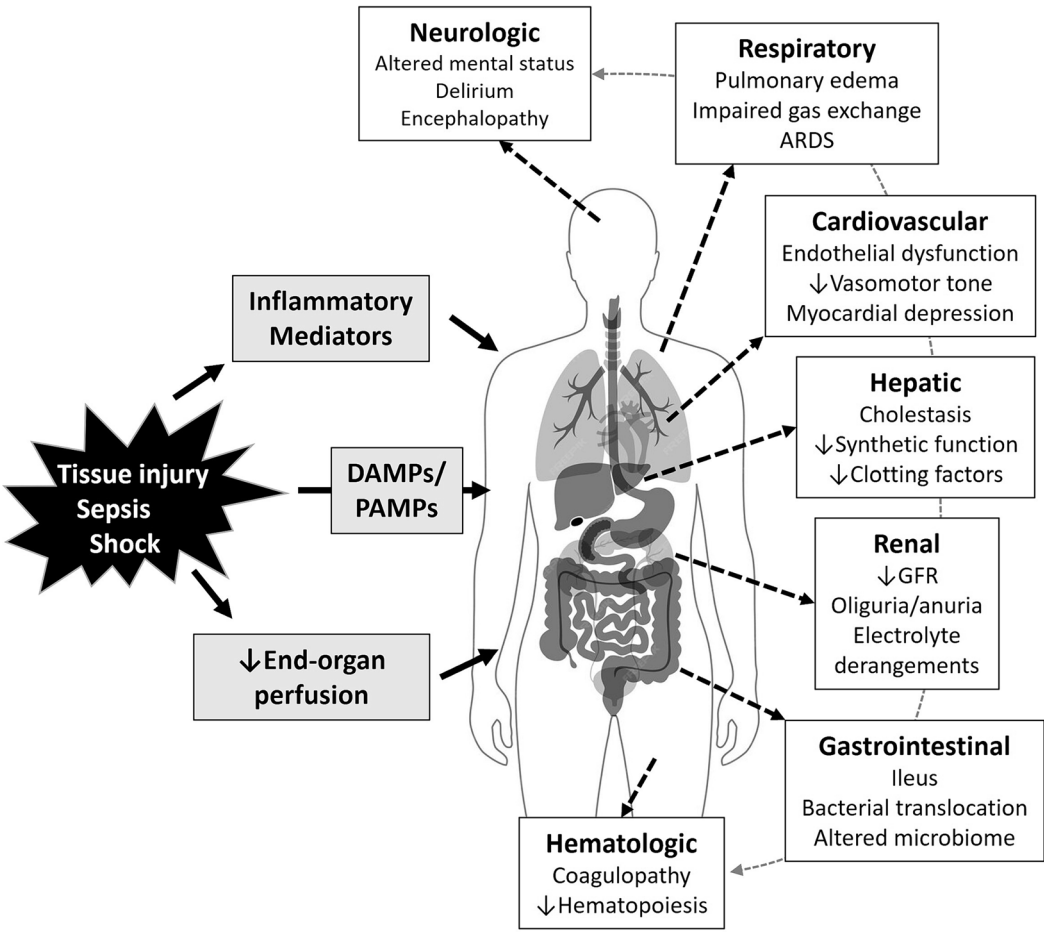

Figure 1. Mechanisms and end-organ manifestations of MOF. Tissue injury, infection and shock trigger the release of inflammatory mediators, damage (DAMPs) and pathogen associated molecular pattern (PAMPs) molecules into the systemic circulation and precipitate MOF. Organ crosstalk from failing organs spreads and perpetuates dysfunction across multiple organ systems.

and organ damage through enhanced inflammatory responses and oxidative stress.[17,18] The pathophysiology of both MOF and CCI involves a complex cascade of inflammatory reactions, immune system imbalances, and microvascular disturbances, culminating in endothelial dysfunction, tissue hypoperfusion, and organ injury.[7] End-organ cellular injury, characterized by mitochondrial dysfunction, oxidative stress, and apoptosis, lies at the core of these conditions, with the relentless release of damage-associated molecular pattern molecules that perpetuate the inflammatory cycle.[19] Organ crosstalk through molecular mediators further amplifies the systemic nature of MOF and CCI, underscoring the interconnectedness of MOF across organ systems.[20,21]

IMMUNE AND INFLAMMATORY PROCESSES IN MOF

Molecular Mediators and Pathways

A key hallmark of MOF is the "cytokine storm," characterized by excessive production of proinflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines.[16,22,23] This cytokine surge can precipitate systemic inflammation, capillary leak syndrome, and subsequent multi-organ damage. Reactive oxygen species (ROS), produced by activated immune cells, play a "double-edged sword" role: essential in microbial killing, but also central in generating oxidative stress and inflicting host cell damage. Furthermore, the interplay between inflammation and coagulation cascades exacerbates organ dysfunction, with proinflammatory cytokines activating coagulation pathways and contributing to conditions like disseminated intravascular coagulation (DIC) and venous thromboembolism.[24,25]

Cellular Response and Immune Dynamics

The immune system's complexity is vividly illustrated by the interactions between endothelial cells and monocytes in response to inflammation. Endothelial cells, by expressing adhesion molecules like vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 and secreting chemokines, crucially orchestrate the recruitment of monocytes to sites of local inflammation.[26] These monocytes undergo phenotypic transformations and can differentiate into macrophages or dendritic cells, depending on the local microenvironment.[27] This recruitment and subsequent differentiation are pivotal for both initiating and propagating the inflammatory response that drives MOF.[14]

In addition to the recruitment of circulating mononuclear cells, the 'cytokine storm' triggers a state of emergency

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myelopoiesis, which is a rapid expansion of hematopoietic stem and progenitor cells in the bone marrow that are released into the systemic circulation.[28] In the days following injury or sepsis, this expansion and persistence of circulating, immature cells, including early-stage granulocytes and myeloid-derived suppressor cells, drives a state of nonresolving inflammation and dysfunctional adaptive immunity.[29]

As this loss of immune homeostasis progresses, it can become chronic, leading to T-cell exhaustion—a state marked by increased expression of inhibitory receptors such as programmed cell death protein-1 and cytotoxic T-lymphocyte associated protein-4 and reduced effector cell functions.[30,31] This immunoparalysis heightens susceptibility to secondary infections and prolongs inflammation, sustaining MOF and increasing the likelihood of transitioning to a state of CCI. In addition, the formation of neutrophil extracellular traps plays a dual role: while essential in trapping and killing pathogens, they can exacerbate local inflammation, tissue damage and thrombosis, contributing to worsening organ dysfunction.[32]

Influence of the Microbiome

The gut microbiome significantly influences systemic immune responses. Disruptions such as dysbiosis can prompt the translocation of bacteria and endotoxins, stoking systemic inflammation and contributing to organ dysfunction in MOF. Metabolites from the microbiota, like short-chain fatty acids, also modulate immune cell functions and systemic inflammation.[33,34] This suggests that therapeutic strategies targeting the microbiome, or its metabolites could have a future role in the management of MOF.

CLINICAL DIAGNOSIS

The clinical manifestations of MOF are diverse and depend on the organs affected and the underlying causes. Diagnosing MOF involves a combination of astute clinical assessment, laboratory tests, imaging studies, and organ-specific functional tests. A thorough patient history and physical examination are crucial for identifying potential causes and assessing the severity of organ dysfunctions. Laboratory evaluations typically include blood cell counts, electrolyte panels, and markers of inflammation and coagulation, among others. Imaging techniques such as X-rays, computed tomography scans, and ultrasounds are used to assess for radiographic sequelae of organ damage and etiology, while hemodynamic monitoring and specific tests like pulmonary function tests can provide insight into the extent of organ dysfunction.

ORGAN-SPECIFIC MANIFESTATIONS

Organ-specific manifestations in MOF reflect the diverse array of insults and pathophysiological mechanisms underlying this syndrome. Each organ system responds differently to the systemic inflammatory cascade, resulting in a spectrum of dysfunctions and clinical manifestations.

Respiratory failure is a hallmark feature of MOF, with pulmonary dysfunction often progressing to acute respiratory distress syndrome (ARDS).[35] In ARDS, diffuse alveolar damage and increased pulmonary vascular permeability lead to impaired gas exchange, hypoxemia, and hypercarbia. Ultimately, the majority of patients with MOF require endotracheal intubation and mechanical ventilation.

Cardiovascular dysfunction in MOF encompasses a spectrum of physiologic abnormalities, including vasodilation, myocardial depression, and hypotension. Despite adequate intravascular volume resuscitation, hypotension and shock often persist in the setting of MOF. A complex interplay of inflammatory mediators, endothelial dysfunction, and dysregulation of vasomotor tone leads to inadequate tissue perfusion and further worsening of organ dysfunction.[36,37] Sepsis-induced myocardial depression is common, characterized by impaired cardiac contractility and reduced stroke volume, often leading to a confusing and difficult to manage physiology of mixed cardiogenic and distributive shock.

Acute kidney injury is a common complication of MOF, with variable etiologies including ischemia-reperfusion injury, sepsis-induced renal dysfunction, and nephrotoxic insults.[38] Acute kidney injury is characterized by a decline in glomerular filtration rate, oliguria or anuria, and electrolyte abnormalities. Renal replacement therapy, including continuous renal replacement therapy or intermittent hemodialysis, may be necessary to support renal function, manage fluid status, and correct electrolyte imbalances.

Hepatic dysfunction in MOF can result in impaired synthetic function, coagulopathies, and hepatic encephalopathy.[39] Reduced hepatic blood flow and hepatocellular injury contribute to impaired synthesis of procoagulant and anticoagulant factors, leading to coagulopathies and increased risk of bleeding and clotting. However, liver dysfunction is often insidious, presenting with more subtle findings such as moderately abnormal liver function tests and a clinical picture of cholestasis. Hepatic encephalopathy, characterized by alterations in mental status and cognitive function, results from the accumulation of neurotoxic substances due to impaired hepatic clearance.

Neurological dysfunction in MOF manifests across a wide range of cognitive impairment, including delirium and coma. Sepsis-associated encephalopathy, with delirium or coma, is a common neurological manifestation and has a clear association with increased mortality. It is important to remember that acute mental status changes or the onset of delirium are often the first sign of decreased end-organ perfusion and incipient MOF.

Gastrointestinal dysfunction in MOF is characterized by mucosal ischemia, barrier dysfunction, and gut dysmotility.[40] Ischemia-reperfusion injury and systemic inflammation compromise gut barrier integrity, leading to bacterial translocation and systemic infection. Gut dysmotility, characterized by ileus or delayed gastric emptying, contributes to feeding intolerance and increased risk of aspiration pneumonia.

Hematological abnormalities in MOF include thrombocytopenia, DIC, and anemia. Disseminated intravascular coagulation, a consumptive coagulopathy characterized by widespread activation of coagulation and fibrinolysis, contributes to microvascular thrombosis, organ dysfunction, and bleeding complications. Persistent thrombocytopenia and anemia are common in patients with chronic critical illness and are a consequence of bone marrow dysfunction driven by circulating catecholamines and inflammatory mediators.[41,42]

Overall, organ-specific manifestations in MOF reflect the complex interplay of inflammatory, immune, and microvascular

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dysregulation, highlighting the systemic nature of this syndrome. Thus, comprehensive management strategies focused on organ support and recovery are essential to improve outcomes and mitigate the progression of MOF in critically ill patients.

MANAGEMENT AND TREATMENT STRATEGIES

Management and treatment of MOF require a comprehensive and multidisciplinary approach aimed at addressing the underlying causes, supporting failing organ system functions, and preventing further deterioration. Early recognition of MOF and prompt initiation of appropriate interventions are crucial in optimizing patient outcomes.

The management of MOF begins with identifying and treating the inciting etiology. For instance, in the setting of sepsis, prompt administration of broad-spectrum antibiotics and source control measures are essential to halt the progression of infection and systemic inflammation. Similarly, in cases of severe trauma and hemorrhagic shock, rapid control of bleeding with blood-based resuscitation strategies and hemostatic interventions are implemented to mitigate ongoing tissue damage.

Supportive care measures play a pivotal role in stabilizing the physiology of patients with MOF and preventing further organ dysfunction. Mechanical ventilation is tailored to support oxygenation and ventilation while minimizing ventilator-induced lung injury. Lung-protective ventilation strategies, including low tidal volume ventilation and minimization of barotrauma, are considered standard-of-care management to mitigate ventilator-associated lung injury.[43] In addition, prone positioning and neuromuscular blockade are often integrated in ARDS management protocols as they have been shown to decrease ARDS-associated mortality.[44,45] Further advanced management strategies, including pulmonary vasodilators, and extracoporal membrane oxygenation, may be necessary in those with critical hypoxia or refractory hypercarbia and acidosis.[46]

Hemodynamic optimization is critical in maintaining adequate tissue perfusion and preventing cardiovascular collapse. Intravascular volume assessment is challenging in patients with MOF. Point-of-care echocardiology has emerged as a key tool to help assess intravascular volume status and differentiate between types of shock (e.g., cardiogenic, hypovolemic, etc.).[47] Once volume status is optimized, vasopressor therapy, such as norepinephrine or vasopressin, is titrated to achieve target mean arterial pressure and restore organ perfusion. Inotropic agents, such as dobutamine or milrinone, may be used to improve cardiac contractility and cardiac output in patients with a component of cardiogenic shock.

Renal replacement therapy (RRT) is instituted in cases of acute renal failure to support kidney function, manage fluid status, and treat electrolyte imbalances. Continuous RRT is preferred in hemodynamically unstable patients, providing gradual fluid removal and metabolic control while minimizing hemodynamic fluctuations.

In patients without significant chronic liver disease, hepatic dysfunction is usually self-limited if secondary insults are avoided. In cases of severe hepatic dysfunction contributing to MOF, supportive measures such as correction of coagulopathy with plasma transfusion or vitamin K supplementation may be necessary. In addition, liver support devices, such as albumin dialysis or molecular adsorbent recirculating system, may be utilized to remove toxins and maintain metabolic homeostasis.

Neurological complications in MOF, such as delirium or coma, require meticulous management to prevent secondary brain injury. Sedation protocols and delirium monitoring tools are implemented to optimize sedation levels and minimize adverse effects. In addition, seizure prophylaxis and neuroprotective strategies may be employed in patients at risk of intracranial hypertension or cerebral edema.

The "holy grail" of using immunomodulating drugs to prevent or reverse MOF remains elusive. Currently, pharmacological interventions targeting inflammation, coagulation, and hemodynamics are included in the management of MOF. Corticosteroids remain controversial and are used in some cases of ARDS to reduce pulmonary inflammation and prevent chronic fibroproliferative changes, or to support relative adrenal insufficiency in the setting of refractory shock states with persistent vasopressor requirements.[48,49] Anticoagulants or antiplatelet agents are administered to prevent thromboembolic complications, particularly in patients with coagulopathy or endothelial dysfunction.

Finally, nutritional support, enteral or parenteral, is essential in meeting metabolic demands and preventing malnutrition in critically ill patients with MOF. Close monitoring of fluid balance, electrolyte status, and nutritional intake is paramount to prevent complications such as fluid overload or electrolyte disturbances.

PROGNOSIS AND OUTCOMES

The prognosis of MOF is influenced by various factors, including the underlying etiology, severity of organ dysfunction, response to treatment, demographics, and presence of comorbidities. Despite advancements in critical care management, MOF remains associated with high morbidity and mortality rates, posing a significant challenge to healthcare professionals.

Factors influencing the prognosis of MOF include the underlying cause of the syndrome. Sepsis-induced MOF carries a poorer prognosis compared with MOF secondary to other etiologies such as trauma or major surgery. The virulence of the causative organism, adequacy of source control, and promptness of antimicrobial therapy impact the prognosis in sepsis-induced MOF. In additiona, the severity of organ dysfunction, as assessed by scoring systems, serves as a prognostic indicator (Table 1).[50] Higher Sequential Organ Failure Assessment (SOFA) scores correlate with increased mortality rates and poorer outcomes in patients with MOF. Persistent organ dysfunction despite treatment is the hallmark of a transition to CCI and is associated with poor long-term outcomes.[51]

Furthermore, the response to initial resuscitative measures and supportive interventions significantly influences the prognosis of MOF. Patients who demonstrate a favorable response, with improvement in organ function and resolution of systemic inflammation, have a better prognosis compared with those with refractory organ dysfunction and ongoing hemodynamic instability. In addition, advanced age or the presence of underlying comorbidities complicates the prognosis of MOF. Pre-existing

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TABLE 1. Scoring Systems Used and/or Developed for Evaluation and Prognosis of Multiple Organ Failure

Scoring System	Focus	Methodology	Application	Pros	Cons
SOFA score	Evaluates the status of six organ systems: respiratory, cardiovascular, hepatic, coagulation, renal, and neurological.	Assigns a score from 0 (normal function) to 4 (high degree of dysfunction) for each organ system, based on specific clinical parameters and laboratory results.	Originally designed to describe organ dysfunction over time in sepsis patients, the SOFA score is now widely used to assess the severity and progression of multiple organ failure in various critical illnesses.	Good predictive validity for patient outcomes and is simple to use.	Does not fully capture all aspects of organ dysfunction, particularly in chronic conditions affecting organ function.
Multiple Organ Dysfunction Score (MODS)	Quantifies the degree of dysfunction in six organ systems similar to SOFA but uses slightly different criteria and scales.	Combines measurements of pulmonary, renal, hepatic, cardiovascular, neurological, and hematological function to calculate a total score.	Used for assessing the severity of organ dysfunction in critically ill patients, MODS helps in predicting mortality and guiding treatment decisions.	Incorporates a broader range of parameters than some other scores, potentially offering a more comprehensive assessment.	Complex to calculate, requiring more detailed laboratory and clinical data.
APACHE score	Assesses the severity of disease in adult patients admitted to intensive care units. APACHE IV is the latest version, incorporating more variables and updated statistical methods.	Evaluates a wide range of physiological parameters, previous health status, and some laboratory results to predict the risk of mortality.	Not exclusively designed for multiple organ failure, APACHE IV can assess the severity of critical illness, including organ dysfunction.	Provides a detailed and comprehensive assessment that can predict hospital mortality with reasonable accuracy.	Underlying complexity and the large number of variables make it time-consuming and less practical for routine clinical use.
Logistic Organ Dysfunction System (LODS)	Assesses the degree of organ dysfunction in critically ill patients.	It scores six organ systems, similar to SOFA and MODS, but uses logistic regression to predict mortality.	Primarily used in research settings, it helps in the stratification of critically ill patients according to their risk of death.	Provides a statistically rigorous method for predicting outcomes.	Complex to calculate and more suited for research than everyday clinical use.

organ dysfunction and impaired physiological reserve predispose patients to a higher risk of mortality and poorer outcomes.

Advancements in critical care support therapies and shock resuscitation have led to significantly decreased early deaths from fulminant MOF after trauma or sepsis. However, initial survivors of MOF often experience persistent organ failure, with residual impairment in organ function even after successful treatment of the inciting cause. This state of persistent organ dysfunction and a prolonged critical illness seen with CCI, is now the predominant phenotype of morbidity and mortality after MOF. Chronic critical illness is associated with an underlying syndrome of persistent inflammation, immunosuppression and catabolism (PICS).[8] These "MOF survivors" suffer from muscle wasting, the inability to physically rehabilitate, recurrent bouts of infection, and commonly succumb to sepsis recidivism and recurrent MOF.[51] (Fig. 2) Long-term complications such as physical disability, cognitive impairment, and psychological distress often persist even after discharge from the intensive care unit. Multiple organ failure patients that develop CCI have a high risk of post-discharge complications, and poor long-term outcomes.

Predicting outcomes in individual patients requires consideration of multiple factors and careful clinical judgment, as MOF is a dynamic syndrome characterized by fluctuations in organ function and clinical status over time. Addressing these challenges requires a holistic approach that integrates prognostic factors, individual patient characteristics, and ongoing clinical assessment to optimize patient outcomes and enhance survivorship in MOF.

PREDICTION AND PREVENTION STRATEGIES

Prediction and prevention of MOF are critical components of managing critically ill surgical patients, aimed at identifying individuals at high risk of developing MOF and implementing interventions to mitigate its occurrence. Predictors of MOF after severe injury, sepsis or major surgery are multi-factorial and related to the severity of the initial insult, a patient's physiologic response, and subsequent complications. The strongest risk factors for MOF after severe trauma include total injury burden, shock severity, total blood product transfusion volume, comorbidity burden and age.[1,52] Similarly in sepsis, the severity of early physiologic derangement, vasopressor refractory shock, comorbidities and advanced age increase the risk of subsequent MOF. Clinical organ failure scores such as the SOFA score and the Acute Physiology and Chronic Health Evaluation (APACHE) score are strongly associated with MOF mortality. These tools can help assess the severity of acute illness and predict the likelihood of subsequent MOF development.

Early recognition of warning signs is crucial in preventing MOF progression. Monitoring for subtle changes in vital signs, laboratory parameters, and clinical symptoms can facilitate early detection. Protocols for regular assessment and documentation of organ function aid in the timely identification of MOF, enabling prompt intervention.[4] Furthermore, emerging technologies such as machine learning and artificial intelligence are being explored to develop predictive models for MOF based on comprehensive clinical, laboratory, and imaging data.[53] Integration of

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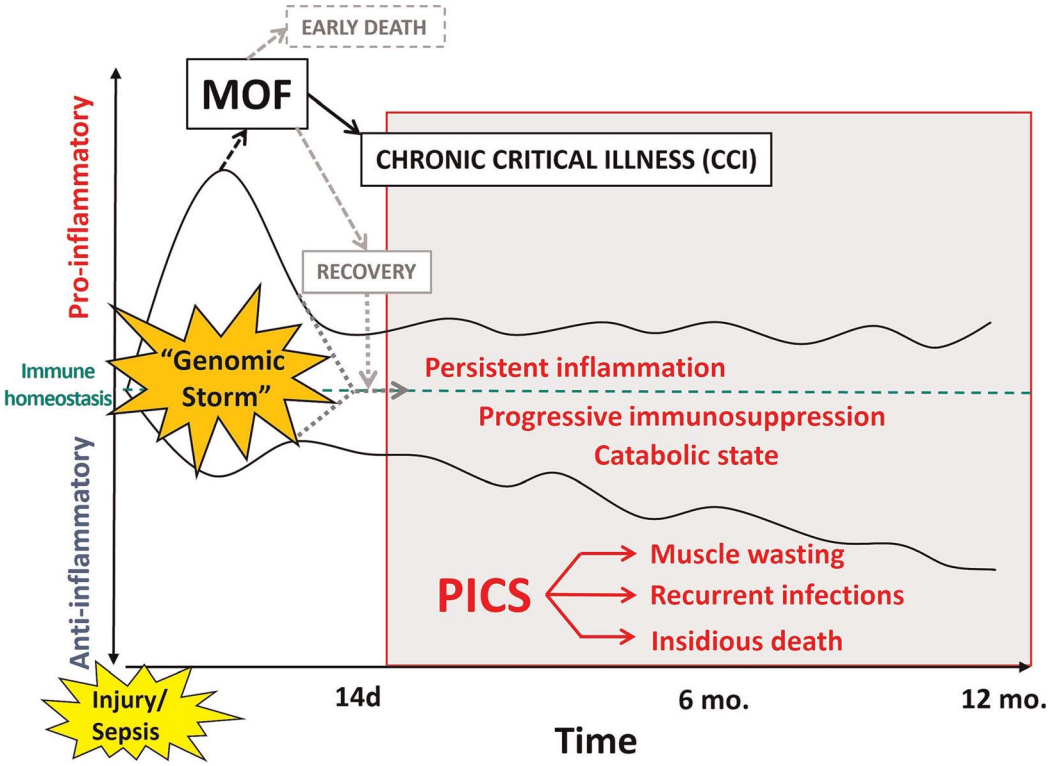

Figure 2. Immune dysregulation, MOF, CCI, and the persistent inflammation, immunosuppression and catabolism syndrome (PICS). Trauma, sepsis or surgical injury triggers a "genomic storm" of immune gene expression in circulating peripheral leukocytes that can trigger MOF. The predominant trajectory of morbidity and mortality of MOF has transitioned from early death, to survival with CCI, and dismal long-term outcomes.

genomic and proteomic biomarkers may enhance the accuracy of these models, enabling personalized risk assessment and early intervention.[6,54]

In the realm of prevention, a proactive approach involves a high index of suspicion, early recognition, and prompt treatment of underlying causes predisposing patients to MOF. Hemorrhage, infection, or hypoperfusion warrant prompt intervention to mitigate the risk of MOF development. Implementation of infection control measures and antimicrobial stewardship programs is vital in reducing the incidence of healthcare-associated infections and subsequent sepsis-induced MOF. Moreover, optimizing hemodynamic parameters through goal-directed therapy and judicious use of vasopressors helps maintain tissue perfusion and oxygen delivery, particularly in shock states. A multidisciplinary approach, involving collaboration between various healthcare professionals, is essential in MOF prevention. By integrating predictive models, early recognition strategies, and targeted prevention interventions, healthcare teams can effectively mitigate the risk of MOF and improve patient outcomes. Continued research and innovation are vital to advancing our understanding of MOF and enhancing our ability to prevent and treat this devastating syndrome.

FUTURE DIRECTIONS

The future of diagnosing, predicting, and managing MOF is likely to be profoundly impacted by advances in medical technology, personalized medicine, and a deeper understanding of the pathophysiology underlying the condition. A speculative summary considering the current trends and potential future advancements includes:

Diagnosing and Predicting Multiple Organ Failure

In the future, the diagnosis of MOF might rely heavily on novel biomarker panels and real-time monitoring systems. Innovations such as nanotechnology and lab-on-a-chip devices could allow for continuous, noninvasive monitoring of organ function, detecting early signs of failure more accurately and rapidly than current methods. Genomic, proteomic, and metabolomic profiling could enable clinicians to identify patients at higher risk of MOF, tailoring preventive strategies to an individual patient's genetic and molecular characteristics.[6,11,55–57] Biomarkers may play a pivotal role in early detection, risk stratification, and management of MOF and CCI. Traditional markers like C-reactive protein and procalcitonin have been supplemented by more specific indicators such as IL-6, TNF-α, and novel markers like circulating cell-free DNA.[11] These biomarkers offer insights into the underlying inflammatory processes, tissue damage, and the body's response to stress and infection.

Artificial intelligence and machine learning models are expected to revolutionize the prediction of MOF.[58,59] These models can integrate vast datasets, including electronic health records, imaging studies, and "-omics" data, to identify subtle patterns and predictors of organ failure that are not apparent to human clinicians. This could facilitate early intervention strategies and personalized risk assessment. Predictive analytics could

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also be used to model disease progression, offering insights into potential future complications and guiding preemptive therapeutic strategies.

Challenges in integrating these diverse data streams into coherent, clinically actionable insights remain significant. The heterogeneity of MOF and CCI, influenced by factors such as the underlying cause, patient comorbidities, and healthcare interventions, complicates the development of universal biomarkers or predictive models. Future research must focus on longitudinal studies that track biomarker levels, immune phenotypes, proteomic signatures, and genomic profiles over time, combined with advanced computational tools to unravel the complex dynamics of MOF and CCI. However, once these challenges are overcome, this multidimensional approach not only holds the potential for improved risk stratification and early detection, but also to aid in the management and development of novel therapies.

Management of MOF

The management of MOF in the future may be characterized by highly personalized and precise interventions. Advanced pharmacogenomics might allow for medications that are specifically tailored to an individual's genetic makeup, maximizing efficacy while minimizing adverse effects. Cellular and gene therapies could target the underlying causes of organ dysfunction, to reverse organ dysfunction. Regenerative medicine, including stem cell therapy and organ bioengineering, holds the promise of repairing or even replacing damaged organs, potentially reversing organ failure.[60,61]

Challenges and Ethical Considerations

While the future of advancing diagnosis, prediction and treatment of MOF is promising, it is not without challenges. The integration of advanced technologies in clinical practice requires overcoming significant technical, financial, regulatory, and ethical hurdles. Issues such as data privacy, informed consent, and equitable access to cutting-edge treatments must be addressed to ensure that the benefits of these advancements are realized by all segments of the population.

CONCLUSION

For the acute care surgeon, MOF remains a complex and diverse syndrome that is challenging to manage and has profound implications for patient care and outcomes. At its core, the pathophysiology of MOF is driven by a dysfunctional host response to injury, infection, and surgical trauma. Recognition of the patient at-risk, prompt resuscitation from shock, and protocolized intensive care that supports organ function while minimizing secondary injury remain the cornerstones of MOF care. By understanding the etiology, pathophysiology, clinical presentation, diagnosis, management strategies, prognosis, and prevention strategies associated with MOF, healthcare professionals can optimize patient care and outcomes. Continued research and advancements in critical care medicine are essential in addressing the unmet needs of patients with MOF and reducing the burden of this devastating condition and its associated long-term complications.

AUTHORSHIP

S.B., L.K., and J.C. were responsible for writing, and for critical revisions.

DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D902).

REFERENCES

1. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. *Crit Care Med*. 2012;40(4):1129–1135.
2. Treml RE, Katayama HT, Caldonazo T, Pereira TS, Malbouisson LMS, Carmona MJC, et al. Perioperative organ dysfunction: a burden to be countered. *Braz J Anesthesiol*. 2024;74(2):844480.
3. Ting RS, Lewis DP, Yang KX, Nguyen TA, Sarrami P, Daniel L, et al. Incidence of multiple organ failure in adult polytrauma patients: a systematic review and meta-analysis. *J Trauma Acute Care Surg*. 2023;94(5):725–734.
4. Cuschieri J, Johnson JL, Sperry J, West MA, Moore EE, Minei JP, et al. Benchmarking outcomes in the critically injured trauma patient and the effect of implementing standard operating procedures. *Ann Surg*. 2012;255(5):993–999.
5. Mira JC, Cuschieri J, Ozrazgat-Baslanti T, Wang Z, Ghita GL, Loftus TJ, et al. The epidemiology of chronic critical illness after severe traumatic injury at two level-one trauma centers. *Crit Care Med*. 2017;45(12):1989–1996.
6. Raymond SL, Hawkins RB, Wang Z, Mira JC, Stortz JA, Han F, et al. Prospective validation of a transcriptomic metric in severe trauma. *Ann Surg*. 2020;271(5):802–810.
7. Efron PA, Brakenridge SC, Mohr AM, Barrios EL, Polcz VE, Anton S, et al. The persistent inflammation, immunosuppression, and catabolism syndrome 10 years later. *J Trauma Acute Care Surg*. 2023;95(5):790–799.
8. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. *J Trauma Acute Care Surg*. 2012;72(6):1491–1501.
9. Kozlov AV, Grillari J. Pathogenesis of multiple organ failure: the impact of systemic damage to plasma membranes. *Front Med (Lausanne)*. 2022;9:806462.
10. Brakenridge SC, Phelan HA, Henley SS, Golden RM, Kashner TM, Eastman AE, et al. Early blood product and crystalloid volume resuscitation: risk association with multiple organ dysfunction after severe blunt traumatic injury. *J Trauma*. 2011;71(2):299–305.
11. Cuschieri J, Bulger E, Schaeffer V, Sakr S, Nathens AB, Hennessy L, et al. Early elevation in random plasma IL-6 after severe injury is associated with development of organ failure. *Shock*. 2010;34(4):346–351.
12. Horn DL, Bettcher LF, Navarro SL, Pascua V, Neto FC, Cuschieri J, et al. Persistent metabolomic alterations characterize chronic critical illness after severe trauma. *J Trauma Acute Care Surg*. 2021;90(1):35–45.
13. Rajicic N, Cuschieri J, Finkelstein DM, Miller-Graziano CL, Hayden D, Moldawer LL, et al. Identification and interpretation of longitudinal gene expression changes in trauma. *PloS One*. 2010;5(12):e14380.
14. Brakenridge SC, Wang Z, Cox M, Raymond S, Hawkins R, Darden D, et al. Distinct immunologic endotypes are associated with clinical trajectory after severe blunt trauma and hemorrhagic shock. *J Trauma Acute Care Surg*. 2021;90(2):257–267.
15. Stortz JA, Hawkins RB, Holden DC, Raymond SL, Wang Z, Brakenridge SC, et al. Cell-free nuclear, but not mitochondrial, DNA concentrations correlate with the early host inflammatory response after severe trauma. *Sci Rep*. 2019;9(1):13648.
16. Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, et al. A genomic storm in critically injured humans. *J Exp Med*. 2011;208(13):2581–2590.
17. Sarma D, Jentzer JC. Cardiogenic shock: pathogenesis, classification, and management. *Crit Care Clin*. 2024;40(1):37–56.
18. Dominguez JH, Xie D, Kelly KJ. Impaired microvascular circulation in distant organs following renal ischemia. *PloS One*. 2023;18(6):e0286543.
19. Hawkins RB, Raymond SL, Stortz JA, Horiguchi H, Brakenridge SC, Gardner A, et al. Chronic critical illness and the persistent inflammation, immunosuppression, and catabolism syndrome. *Front Immunol*. 2018;9:1511.

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20. Efron PA, Mohr AM, Bihorac A, Horiguchi H, Hollen MK, Segal MS, et al. Persistent inflammation, immunosuppression, and catabolism and the development of chronic critical illness after surgery. *Surgery*. 2018;164(2):178–184.
21. Vanzant EL, Lopez CM, Ozrazgat-Baslanti T, Ungaro R, Davis R, Cuenca AG, et al. Persistent inflammation, immunosuppression, and catabolism syndrome after severe blunt trauma. *J Trauma Acute Care Surg*. 2014;76(1):21–29 discussion 9-30.
22. Chakraborty RK, Burns B. Systemic Inflammatory Response Syndrome. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Bracken Burns declares no relevant financial relationships with ineligible companies. 2024.
23. Riyaz Tramboo S, Elkhalifa AME, Quibtiya S, Ali SI, Nazir Shah N, Taifa S, et al. The critical impacts of cytokine storms in respiratory disorders. *Heliyon*. 2024;10(9):e29769.
24. Kornblith LZ, Moore HB, Cohen MJ. Trauma-induced coagulopathy: the past, present, and future. *J Thromb Haemost*. 2019;17(6):852–862.
25. Moore EE, Moore HB, Kornblith LZ, Neal MD, Hoffman M, Mutch NJ, et al. Trauma-induced coagulopathy. *Nat Rev Dis Primers*. 2021;7(1):30.
26. Bertram K, Cox C, Alam H, Lowell C, Cuschieri J, Parekkadan B, et al. Insights from CTTACC: immune system reset by cellular therapies for chronic illness after trauma, infection, and burn. *Cytotherapy*. 2024.
27. Cuschieri J, Kornblith L, Pati S, Piliponsky A. The injured monocyte: the link to chronic critical illness and mortality following injury. *J Trauma Acute Care Surg*. 2024;96(2):195–202.
28. Kelly LS, Darden DB, Fenner BP, Efron PA, Mohr AM. The hematopoietic stem/progenitor cell response to hemorrhage, injury, and sepsis: a review of pathophysiology. *Shock*. 2021;56(1):30–41.
29. Rincon JC, Efron PA, Moldawer LL. Immunopathology of chronic critical illness in sepsis survivors: role of abnormal myelopoiesis. *J Leukoc Biol*. 2022;112(6):1525–1534.
30. Riva A, Chokshi S. Immune checkpoint receptors: homeostatic regulators of immunity. *Hepatol Int*. 2018;12(3):223–236.
31. Ghnewa YG, Fish M, Jennings A, Carter MJ, Shankar-Hari M. Goodbye SIRS? Innate, trained and adaptive immunity and pathogenesis of organ dysfunction. *Med Klin Intensivmed Notfmed*. 2020;115(Suppl 1):10–14.
32. Abrams ST, Morton B, Alhamdi Y, Alsabani M, Lane S, Welters ID, et al. A novel assay for neutrophil extracellular trap formation independently predicts disseminated intravascular coagulation and mortality in critically ill patients. *Am J Respir Crit Care Med*. 2019;200(7):869–880.
33. Baue AE. Nutrition and metabolism in sepsis and multisystem organ failure. *Surg Clin North Am*. 1991;71(3):549–565.
34. Corriero A, Gadaleta RM, Puntillo F, Inchingolo F, Moschetta A, Brienza N. The central role of the gut in intensive care. *Crit Care*. 2022;26(1):379.
35. Ramji HF, Hafiz M, Altaq HH, Hussain ST, Chaudry F. Acute respiratory distress syndrome; a review of recent updates and a glance into the future. *Diagnostics (Basel)*. 2023;13(9):1528.
36. Garrison RN, Spain DA, Wilson MA, Keelen PA, Harris PD. Microvascular changes explain the "two-hit" theory of multiple organ failure. *Ann Surg*. 1998;227(6):851–860.
37. Martin L, Derwall M, Al Zoubi S, Zechendorf E, Reuter DA, Thiemermann C, et al. The septic heart: current understanding of molecular mechanisms and clinical implications. *Chest*. 2019;155(2):427–437.
38. Lara-Prado JI, Pazos-Perez F, Mendez-Landa CE, Grajales-Garcia DP, Feria-Ramirez JA, Salazar-Gonzalez JJ, et al. Acute kidney injury and organ dysfunction: what is the role of uremic toxins? *Toxins (Basel)*. 2021;13(8):551.
39. Gourd NM, Nikitas N. Multiple organ dysfunction syndrome. *J Intensive Care Med*. 2020;35(12):1564–1575.
40. Lawson CM, Jones C, Herman M, Kim C, Mannino E, Omer E, et al. Does ileus represent the forgotten end organ failure in critical illness? *Curr Gastroenterol Rep*. 2024;26:166–171.
41. Loftus TJ, Mira JC, Stortz JA, Ozrazgat-Baslanti T, Ghita GL, Wang Z, et al. Persistent inflammation and anemia among critically ill septic patients. *J Trauma Acute Care Surg*. 2019;86(2):260–267.
42. Apple CG, Miller ES, Kannan KB, Thompson C, Darden DB, Efron PA, et al. Prolonged chronic stress and persistent iron dysregulation prevent anemia recovery following trauma. *J Surg Res*. 2021;267:320–327.
43. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301–1308.
44. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159–2168.
45. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107–1116.
46. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195(9):1253–1263.
47. Levitov A, Frankel HL, Blaivas M, Kirkpatrick AW, Su E, Evans D, et al. Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients—part II: cardiac ultrasonography. *Crit Care Med*. 2016;44(6):1206–1227.
48. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med*. 2017;43(12):1751–1763.
49. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med*. 2018;378(9):797–808.
50. Fan S, Ma J. The value of five scoring systems in predicting the prognosis of patients with sepsis-associated acute respiratory failure. *Sci Rep*. 2024;14(1):4760.
51. Brakenridge SC, Efron PA, Cox MC, Stortz JA, Hawkins RB, Ghita G, et al. Current epidemiology of surgical sepsis: discordance between inpatient mortality and 1-year outcomes. *Ann Surg*. 2019;270(3):502–510.
52. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. *J Trauma Acute Care Surg*. 2013;74(3):774–779.
53. Loftus TJ, Tighe PJ, Filiberto AC, Efron PA, Brakenridge SC, Mohr AM, et al. Artificial intelligence and surgical decision-making. *JAMA Surg*. 2020;155(2):148–158.
54. Brakenridge SC, Starostik P, Ghita G, Midic U, Darden D, Fenner B, et al. A transcriptomic severity metric that predicts clinical outcomes in critically ill surgical sepsis patients. *Crit Care Explor*. 2021;3(10):e0554.
55. Cobb JP, Moore EE, Hayden DL, Minei JP, Cuschieri J, Yang J, et al. Validation of the riboleukogram to detect ventilator-associated pneumonia after severe injury. *Ann Surg*. 2009;250(4):531–539.
56. Cuenca AG, Gentile LF, Lopez MC, Ungaro R, Liu H, Xiao W, et al. Development of a genomic metric that can be rapidly used to predict clinical outcome in severely injured trauma patients. *Crit Care Med*. 2013;41(5):1175–1185.
57. Cook AC, Joseph B, Mohler MJ, Inaba K, Bruns BR, Nakonezny PA, et al. Validation of a geriatric trauma prognosis calculator: a P.A.L.Li.A.T.E. Consortium study. *J Am Geriatr Soc*. 2017;65(10):2302–2307.
58. Lal A, Li G, Cubro E, Chalmers S, Li H, Herasevich V, et al. Development and verification of a digital twin patient model to predict specific treatment response during the first 24 hours of sepsis. *Crit Care Explor*. 2020;2(11):e0249.
59. An G, Cockrell RC. Agent-based modeling of systemic inflammation: a pathway toward controlling Sepsis. *Methods Mol Biol*. 2021;2321:231–257.
60. Hu J, Li Y, He J, Zhao X, Chen M, Ye L, et al. Mesenchymal stromal/stem cells: breaking the deadlock in the treatment of multiple organ dysfunction syndrome. *Chin Med J (Engl)*. 2022;135(23):2818–2820.
61. Kandula UR, Wake AD. Effectiveness of RCTs pooling evidence on mesenchymal stem cell (MSC) therapeutic applications during COVID-19 epidemic: a systematic review. *Biologics*. 2023;17:85–112.

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